

JNJ-65355394: A Chemical Probe for OGA

Version 1.0 (21th October 2021)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!/specificprobeoverview/JNJ-65355394>

Overview

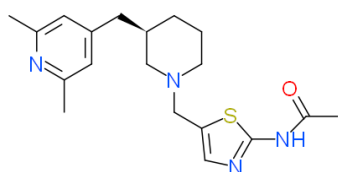
OGA, a member of the family of hexosaminidases, catalyzes the removal of the O-GlcNAc post-translational modification from serine and threonine. OGA activity is the highest at neutral pH and it localizes mainly to the cytosol. O-GlcNAc plays an important role in the aggregation of the tau protein as found in neurodegenerative disorders, such as Alzheimer's disease, Pick's disease, and Parkinson's disease. O-GlcNAcylated tau protein displays improved stability and solubility compared with its unmodified state, which in turn leads to a suppression of the aggregation of the tau protein. Therefore, inhibition of OGA may prevent the formation of aggregations.

Summary

Chemical Probe Name	JNJ-65355394
Negative control compound	JNJ-73924149
Target(s) (synonyms)	OGA (O-GlcNAcase, Nuclear cytoplasmic O-GlcNAcase and acetyltransferase, NCOAT, HEXC, MGEA5, MEA5)
Recommended <i>in vitro</i> assay concentration	Use at concentration up to 10 μ M for JNJ-65355394 and JNJ-73924149; use with control and orthogonal probe for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	JNJ-65355394 blocks OGA in mouse brain after single p.o. gavage administration (100 mg/kg).
Publications	WO2018109202A1
Orthogonal chemical probes	TP-040
<i>In vitro</i> assay(s) used to characterise	Fluorescence-based enzymatic assay
Cellular assay(s) for target-engagement	Cell-based OGA assay

Chemical Probe & Negative Control Structures and Use

JNJ-65355394 Chemical Probe



SMILES: CC(Nc1ncc(CN2CCC[C@H](Cc3cc(C)nc(C)c3)C2)s1)=O

InChiKey: CYFBRQHYEQKYHH-MRXNPFEDSA-N

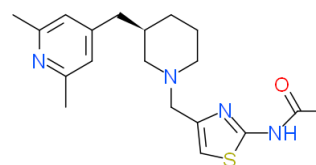
Molecular weight: 358.18 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

JNJ-73924149 Negative Control



SMILES: CC(Nc1ncc(CN2CCC[C@H](Cc3cc(C)nc(C)c3)C2)cs1)=O

InChiKey: VKYYOTCDIVOPRO-MRXNPFEDSA-N

Molecular weight: 358.18 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

JNJ-65355394 shows potent activity on OGA in a fluorescence-based enzymatic assay (IC_{50} = 1.3 nM) and no activity on HEXA (IC_{50} > 10 μ M). Closest hits in the CEREP panel (54 at 10 μ M) are [% inhibition]: rat OPRK1 (78), rat ADORA2A (69) and human OPRM1 (55).

Potency in Cells and Cellular Target Engagement:

JNJ-65355394 is active in a cell-based OGA assay (human OGA IC_{50} = 3.9 nM).